REMARKS

Claims 1-22 are pending in the application. Claim 1 has been amended to incorporate the subject matter of Claim 2. Accordingly, Claim 2 has been canceled. Claim 13 has been cancelled as the subject matter of Claim 13 is also incorporated into independent Claim 1. Claims 4 and 15 have been withdrawn as being directed toward a non-elected invention. Applicant understands that these claims will be examined upon allowance of the linking claims (Claim 1 and Claims 5-12, and 16-19 dependent thereon). Claims 20-21 have been cancelled without prejudice.

In the Office Action mailed December 22, 2003, the Examiner took the following actions and imposed the following rejections: the Examiner maintained the restriction requirement and countered Applicant's traversal. The Examiner denied Applicants' claim to the priority of parent application S/N 09/078,954 filed May 14, 1998. Claims 1, 3, 6 and 20 were rejected under §102(e) or 102(b) as being anticipated by U.S. Patent No. 5,703,055 to Felgner *et al.* as evidenced by Bei *et al.* (*J. Immunotherapy*, 21:159-169 (1998)). Claims 1, 3, 5, 7-12, 14, 16, 20 and 21 were rejected under §102(a) or 102(e) as being anticipated by U.S. Patent No. 6,207,646 to Krieg *et al.* Claims 1, 3, 5-12, 14 and 16-21 were further rejected under §103 as being obvious over Felgner *et al.* taken with Krieg *et al.* in view of either U.S. Patent No. 6,143,716 to Meers *et al*, or U.S. Patent No. 5,976,567 to Wheeler *et al.*, and further in view of Applicants' admission of prior art on pages 7 and 11 of the specification. Claims 1, 6, 11 and 17-19 were also rejected as obvious over Krieg *et al.* in view of either Wheeler *et al.* or Meers *et al.* A provisional double patenting rejection was also imposed based on the now-abandoned parent application S/N 09/649,527.

Priority

In view of the Examiner's remarks in the instant application as well as in parent application S/N 09/649,527, Applicant has amended the specification to delete the claim of priority to U.S. Patent Application Ser. No. 09/078,954, filed May 14, 1998 and U.S. Patent Application Ser. No. 08/856,374, filed May 14, 1997. MPEP §201.11 (III) (G).

Restriction Requirement

The claims of the present application were subject to a restriction requirement. The Examiner required the election as between Group I (claims 3 and 14), Group II (claims 2 and 13) and Group III (claims 4 and 15) with claim 1, and claims 5-12, and 16-19 dependent thereon identified as the linking claim between inventions I-III. Applicant elected the claims of Group I with traverse. The traversal was based on the assertion that Group II claims are generic with respect to the claims of Group I, and as such Groups I and II should be examined together.

In response to the Applicant's traversal the Examiner asserts that the phrase "non-sequence specific" as used in previously pending claim 2, and now present in amended claim 1, lacks antecedent basis based on the Examiner's review of page 60, lines 5-10 of the specification, and is exclusive of sequences having a CpG motif or a palindrome in view of the cited disclosure. Applicant respectfully requests reconsideration and directs the Examiner's attention to more pertinent disclosure in the Summary of Invention section of the specification which sets forth both the phrase and the corresponding definition of "non-sequence specific." Specifically, beginning on page 2, line 26, the specification teaches that lipid-nucleic acid particles can provide therapeutic benefits, even when the nucleic acid is not complementary to coding sequences in target cells. The specification then asserts that lipid-nucleic acid particles including these non-sequence specific oligodeoxynucleotides can be used to enhance the immune response. [*See* spec. at page 3, lines 1-3]. Thus, the specification clearly defines "non-sequence specific" oligodeoxynucleotides as being nucleic acids that are not complementary to coding sequences in target cells.

The Summary goes on to describe this embodiment in the context of an inventive method wherein "the nucleic acid included in lipid particle is one which may not bind with *sequence specificity* to particular cells," and further teaches that the nucleic acid "may suitably be one which is non-complementary to the human genome, such that it acts to provide immunostimulation in a manner independent of conventional base–pairing interactions between the nucleic acid and nucleic acids of the treated mammal. [*See* spec. at page 3, lines 11-24].

According to the specification, these non-complementary nucleic acids "may suitably contain an immune–stimulating motif such as a CpG motif, or an immune stimulating palindromic sequence." [*See* spec. at page 3, lines 23-24]. As explained in the Background section, it is an object of the instant invention to further exploit these types of non-complementary immune stimulatory sequences or "ISS" that employ a different mechanism of action in comparison with the more traditional antisense and/or gene expression approaches of sequence-specific oligodeoxynucleotides. [*See* spec. at page 2, lines 3-16]

Consistent disclosure is also found on page 7 of the Detailed Description, which explains that "nucleotide sequences may be complementary to patient/subject mRNA, such as antisense oligonucleotides, or they may be foreign or non-complementary (which means they do not *specifically hybridize* to the patient/subject genome)." [Spec. at p. 7, lines 14-16 (emphasis added)]. Also consistent is the disclosure on page 60, lines 5-10 referenced by the Examiner, which reiterates the preferred embodiment of the invention identified in the Summary as "non-sequence specific," which utilizes "nucleic acids which are not complementary to the genome of the treated mammal, and which provide immunostimulation through a mechanism which does not depend on a complementary base-pairing interaction with nucleic acids of the mammal." As indicated therein, these non-sequence specific nucleic acids can include both CpG motifs and palindromes.

Applicant respectfully submits that the claim phrase "non-sequence specific" does indeed have antecedent basis in the specification and is consistently defined as a nucleic acid or oligodeoxynucleotide which is non-complementary to the target cell genome and thus provides immunostimulation in a manner independent of conventional base–pairing interactions. Thus, the referenced phrase necessarily excludes antisense sequences. Based on the explicit teaching throughout the specification, however, the referenced phrase does not exclude necessarily CpG or other immunostimulatory motifs, since these types of ISS do not function by way of a deliberate base-pairing interaction within the target cell. Applicant has amended Claim 1 in accordance with these teachings to recite an immunostimulatory composition comprising an oligodeoxynucleotide fully encapsulated in a lipid particle comprising a cationic lipid, wherein the oligodeoxynucleotide is a <u>non-sequence specific</u> immunostimulatory sequence, and

respectfully requests that the Examiner reconsider his proposed interpretation and restriction in light of the foregoing. Claim 3 depends from Claim 1 and recites a non-sequence specific oligodeoxynucleotide that contains a CpG motif. Applicant asserts that is proper to examine all pending claims together.

As explained in more detail below, Claim 1 was further amended to include the term "fully" encapsulated. Support for this amendment is found throughout the specification. Specifically, on page 16, lines 16-23, the specification expressly defines "fully encapsulated".

Applicants' Invention

In the interests of crystallizing the issues and resolving an apparent misunderstanding by the Examiner regarding the significant features of the presently-claimed invention, Applicants would like to provide a brief synopsis of their discovery. The present invention is based on the surprising discovery that fully encapsulating a nucleic acid within a liposomal particle results in an improved immunostimulatory composition, even where the nucleic acid is normally non-immunostimulatory in its free form and/or lacks a recognized immunostimulatory motif. [*See, e.g.,* Spec. at pp. 2-3; Example 1, p. 35 & Figure 11; Example 3, p. 43 & Figure 23]. In the case of established non-sequence specific immunostimulatory oligodeoxynucleotides, such as the unmethylated CpG sequences disclosed by Krieg *et al.*, lipid encapsulation according to the subject invention provides a dramatic improvement in the resulting immune response *in vivo*.

Importantly, however, as taught in the specification at, *e.g.,* pages 16-17, the structural characteristics of Applicants' liposomal compositions recited in the claims is critical for these beneficial effects and serves to distinguish them over the prior art, a fact which has been consistently overlooked by the Examiner. Based on the comments and arguments in the office actions to date, the Examiner has ignored the claim limitations relating to the structural characteristics of the presently-claimed compositions and would appear to be focusing solely on the patentability of the basic lipid components. For example, in the most recent office action the Examiner asserts that "[t]he claims are readable on a composition comprising a cationic amphiphile/biologically active molecule (DNA, RNA, polypeptides) contained composition

regardless of the structure of the amphiphile and/or DNA so as to stimulate an immunostimulatory activity in a mammal, so long as the DNA is encapsulated in a lipid particle comprising a cationic lipid." [Office Action mailed 12/22/03, p. 6]. The nature of the prior art combinations proposed by the Examiner (*e.g.*, Wheeler *et al.* and Meers *et al.* for DODMA and DODAP/PEG-lipid/DOPE, respectively) further evidence simple combinations based on the disclosure of certain cationic lipids irrespective of the actual liposomal structures taught by these references.

Applicants respectfully traverse, since the critical aspects of the presently claimed invention are not limited solely to the incorporation of a cationic lipid *per se.* As explained in the accompanying Declaration Pursuant to 37 C.F.R. §1.132 submitted by Dr. Michael J. Hope, one cannot focus only on the basic components of a liposomal delivery vehicle without also considering the structural characteristics of the vehicle formed. This is particularly the case with respect to liposomal delivery of nucleic acids, which at the priority date of the instant case still faced a number of significant hurdles to systemic *in vivo* utility. *See, e.g.*, Hope *et al., Molecular Membrane Biol.* 15:1-14 (1998), attached as Ex. 2 to the accompanying Rule 132 declaration. The submitted declaration speaks to the actual liposomal structures formed by the prior art teachings relied on by the Examiner and contrasts them with those of the presently-claimed invention, and also provides additional scientific data evidencing the critical nature of the described structural differences and their dramatic effect on immune stimulation *in vivo.* Reconsideration of the presently-claimed invention in light of the foregoing clarification and Applicants' newly-presented evidence is respectfully solicited.

The individual rejections in the Office Action mailed 22 December 2003 are discussed in more detail below.

Anticipation and Obviousness

Turning now to the rejections, as noted in the introductory discussion above each of the rejections of the claims for anticipation or obviousness overlooks the "fully encapsulated" limitation recited in the independent claims. This would appear to be based on a mistaken belief that the lipid compositions described in the cited art are structurally and functionally the same as in the instant case. As explained in the accompanying Rule 132 declaration as well as in the

accompanying contemporaneous art references, this is simply not the case. Moreover, there is no teaching or suggestion in the cited prior art including the principal reference of Krieg *et al.* that would lead the skilled artisan to select lipid encapsulation as opposed to lipid complexing of a non-sequence specific immunostimulatory nucleic acid as opposed to one of the other myriad possible delivery vehicles described.

Anticipation by Felgner *et al.* as evidenced by Bei *et al.*

The lipid-nucleic acid compositions described by Felgner *et al.* are lipid nucleic acid "complexes" or aggregates, which are structurally different from nucleic acids encapsulated in lipid particles. [Rule 132 Declaration at ¶¶ 5-8]. As explained in the accompanying declaration, and as described and illustrated in the attached art reference, these lipid-DNA complexes only provide partial encapsulation or coating of the nucleic acid, with consequent problems in serum stability and *in vivo* utility. In contrast, the presently-claimed compositions provide *fully encapsulated* lipid-DNA particles having greater serum stability and dramatically enhanced immunostimulatory activity *in vivo.* [Rule 132 Dec. at ¶¶ 10-15]. Moreover, the compositions proposed by Felgner *et al.* generally employ nucleic acids having coding sequences for genes of interest, in contrast to the present invention in which the fully-encapsulated immunostimulatory oligodeoxynucleotide is non-complementary to coding sequences present in the target cells (*i.e.*, non-sequence specific). [*See* Spec. at p. 2, lines 10-15].

Applicants respectfully submit that the foregoing comments and the submitted declaration clearly rebut the Examiner's assertion that the "claims are readable on a method of employing any cationic amphiphile/biologically active molecule (DNA, RNA, polypeptides) contained composition regardless for the structure of the amphiphile and/or DNA so as to stimulate an immunostimulatory activity in a mammal." [Office Action p. 6 (emphasis added)]. In fact, the claims as presently amended read only on *non-coding* and *non-complementary* oligodeoxynucleotides *fully encapsulated* in a cationic lipid particle, a composition which is neither taught by nor suggested in Felgner *et al.* Since the reference by Bei *et al.* does nothing to correct these shortcomings in the disclosure by Felger *et al.*, withdrawal of this ground of rejection is respectfully requested.

Anticipation by U.S. Patent No. 6,207,646 to Krieg *et al.*

Claims 1, 3, 5, 7-12, 14, 16, 20 and 21 were rejected as anticipated by Krieg *et al.* based on the loose use of the term "encapsulated" in the text cited by the Examiner. For the reference to properly anticipate the presently claimed invention, however, there must be a clear teaching within the four corners of the document of Applicants' claimed invention, as opposed to an ambiguous suggestion of one potential DNA delivery vehicle taken from a laundry list of other completely irrelevant possibilities. Krieg *et al.* provides no such teaching, and in fact provides no teaching or suggestion whatsoever that lipid delivery vehicles (whether encapsulated or complexed) would be any more preferable than any of the other possible DNA delivery vehicles also disclosed.

Krieg *et al* is clearly directed to the field of immunostimulatory nucleic acids *per se* and does not teach anything about lipid/nucleic acid structures. Krieg *et al.* does not cite, or incorporate by reference, any teaching that would enable one to make a fully-encapsulated nucleic acid lipid particle. Moreover, Krieg *et al.* describes a panoply of delivery methods, and provides no basis for selecting lipids as opposed to the sterols or target cell binding agents also proposed. There is certainly no recognition by Krieg *et al.* of the synergistic properties obtained by fully encapsulating an immunostimulatory nucleic acid within a cationic lipid particle. The skilled person would therefore not be motivated by Krieg *et al.* to select lipid encapsulation as an advantageous method of nucleic acid delivery. Moreover, the skilled person would not recognize any difference between lipid encapsulation and lipid complexing of nucleic acid, and would therefore not be motivated from Krieg *et al.* to seek out a method of full lipid encapsulation as opposed to conventional lipid complexing. Indeed, the actual disclosure in Krieg *et al.* would appear to simply intermingle the two terms with no recognition of the distinction between the two. Without a more definitive or pertinent teaching, Krieg *et al.* neither anticipates the present claims, nor renders them obvious.

Accordingly, withdrawal of this ground of rejection is also respectfully requested.

Obviousness over Felgner in view of Meers or Wheeler and Applicants' alleged admission

Claims 1, 3, 5-12, 14 and 16-21 were further rejected as obvious over Felgner *et al.* taken with Krieg *et al.* in view of either Meers *et al*, or Wheeler *et al*, further in view of

Applicants' admission of prior art. The deficiencies of Felgner *et al.* and Krieg *et al.* are discussed above. These deficiencies are not cured by the combination Krieg *et al.,* Meers *et al.* or Wheeler *et al.* As indicated, there is no specific motivation to combine Felgner *et al.* with Krieg *et al.* and, even if combined, the resulting liposomal vehicles are distinguished by the present claims since there is no teaching or suggestion of a lipid particle having a non-sequence specific oligodeoxynucleotide fully encapsulated within it.

Meers *et al.* describe peptide-lipid conjugates and liposomes that have a lipid component that includes the peptide-lipid conjugate. Meers *et al.* mention at column 9, line 46 that the liposomes may comprise a bioactive agent (e.g., DNA). Example 4 teaches making a liposome preparation, but there is no teaching in that example, nor anywhere else in the reference, that the DNA should be fully encapsulated in a liposome particle or how to make the same. There is also no teaching that a lipid encapsulating a nucleic acid as a bioactive agent would be advantageous or that it would be immunostimulatory. Accordingly, the combination of Meers *et al.* with Felgner *et al.* still fails to teach or suggest to one of ordinary skill in the art that a lipid encapsulating a nucleic acid should be made.

Wheeler *et al.* also fails to teach or suggest encapsulating a nucleic acid in a lipid particle. While Wheeler *et al.* teaches particular types of cationic lipids that may used to complex with nucleic acids for lipid mediated nucleic acid delivery, Wheeler *et al.* merely teach making pre-formed cationic liposomes using such cationic lipids and combining them with nucleic acids to form a complex. As stated in the declaration, the complexes made according to Wheeler *et al.* would have essentially the same structure as those made according to Felgner *et al.*, wherein the nucleic acid is not fully encapsulated in the cationic lipid particle.

Accordingly, withdrawal of the rejection of the claims on this ground is also respectfully requested.

Obviousness over Krieg *et al.* in view of either Wheeler *et al.* or Meers *et al.*

Claims 1, 6, 11 and 17-19 were also rejected as obvious over Krieg *et al* in view of either Wheeler *et al* or Meers *et al.* The deficiencies in Krieg, Wheeler and Meers are discussed above. To reiterate in short, there is no teaching or suggestion by Krieg *et al.* to select lipid encapsulation as opposed to lipid complexing as opposed to any other form of DNA

delivery, nor any teaching of how to fully encapsulate a nucleic acid in a lipid, nor any teaching that it could provide synergistic immunostimulatory effects, and there is no reference in Krieg *et al.* to any other teaching regarding the foregoing. Neither Wheeler *et al.* nor Meers *et al.* provides any such teaching or suggestion. Accordingly, withdrawal of this ground of rejection is respectfully requested.

Double Patenting

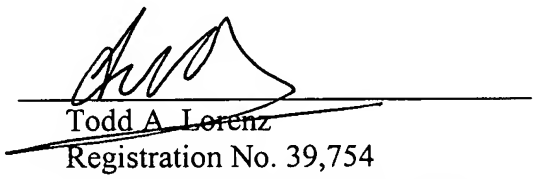
The provisional double patenting rejection has been obviated by the abandonment of the parent case S/N 09/649,527.

All of the claims remaining in the application are now clearly allowable. Favorable consideration and a timely Notice of Allowance are earnestly solicited. If the Examiner has any questions or if an interview would be of benefit in furthering the Examiner's understanding of the characteristics of the claimed liposomal delivery vehicles the Examiner is encouraged to contact the undersigned representative at the number provided.

Respectfully submitted,

DORSEY & WHITNEY LLP

Date 6/22/04



Todd A. Lorenz
Registration No. 39,754
Telephone No. (415) 781-1989

DORSEY & WHITNEY LLP
Four Embarcadero Center, Suite 3400
San Francisco, CA 94111
(415) 781-1989 (telephone)
(415) 398-3249 (fax)

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